Case Study

- 57 year old male, trial application for $1,000,000 Universal Life coverage
- Cover letter from sales agent indicates client has Chronic Lymphocytic Leukemia (CLL) diagnosed in 1999 (age 44), and is on new medication, GA-101, which has been very successful
- Last 3 months of oncology treatment notes sent for review
  - Most recent 5/12 note indicates client with Rai stage II disease, showing improvement in lymphadenopathy, splenomegaly no longer detectable, and elimination of his “B” symptoms after 2 doses of GA-101
  - CBC normal other than slightly low platelet count (144,000/mm³)
Case study, continued

• Oncology records, continued:
  – 3/12 labs, prior to starting GA-101 treatment:
    • Absolute lymphocyte count > 50,000/mm³
    • Platelet count 112,000/mm³
    • β-2 microglobulin 1,746 (no units given; usual normal range is less than 4 mg/L)
  – Prior evaluation included:
    • low CD38 and ZAP-70
    • 13q deletion in the leukemic cells on flourescent in-situ hybridization (FISH) testing
  – 5/12 treatment plan was to continue with planned 3rd dose of GA-101 and return in three weeks
• What are important points in risk assessment of this case?

USA – Estimated Leukemia
New Cases and Deaths in 2012

• CLL is the most common form of leukemia in the USA

<table>
<thead>
<tr>
<th>Type of leukemia</th>
<th>Estimated Cases</th>
<th>Estimated deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphocytic</td>
<td>6,050</td>
<td>1,440</td>
</tr>
<tr>
<td>Chronic lymphocytic</td>
<td>16,060</td>
<td>4,580</td>
</tr>
<tr>
<td>Acute myeloid</td>
<td>13,780</td>
<td>10,200</td>
</tr>
<tr>
<td>Chronic myeloid</td>
<td>5,430</td>
<td>610</td>
</tr>
<tr>
<td>Other leukemias</td>
<td>5,830</td>
<td>6,710</td>
</tr>
<tr>
<td>Totals</td>
<td>47,150</td>
<td>23,540</td>
</tr>
</tbody>
</table>

American Cancer Society
CLL - Epidemiology

- SEER data, 1975 - 2009:
  - Incidence fairly stable @ 4-5/100,000/year
  - M:F ratio about 2:1
  - 5-year relative survival is improving:
    - Diagnosis in 1975 – 1977: 67.4%
    - Diagnosis in 2002 – 2008: 82.4%
- Primarily a disease of older aged persons
  - Median age at diagnosis is 72 yrs
  - 70% of patients are > 65 yrs at time of diagnosis
  - < 2% of patients younger than 45 yrs at diagnosis
- Incidence lower in Asia, Latin America and Africa than in North America and Western Europe

Clinical Presentation

- Many CLL patients asymptomatic, diagnosed on routine CBC
- Painless lymphadenopathy, often cervical area
- Systemic “B” symptoms of lymphoma (5-10%) are unfavorable when present
  - Unintentional weight loss > 10% over 6 mos
  - Fever or drenching night sweats without evidence of infection
  - Extreme fatigue
CLL Pathology

• Etiology unclear
  – 2 – 7X increased risk for family members of CLL patients
  – Possible role of certain agricultural chemicals
  – Monoclonal B-cell lymphocytosis (MBL)
    • Present in about 4% of the population > 40 yrs of age
    • All cases of CLL appear to be preceded by MBL, but most patients with MBL will not develop CLL or any other hematologic malignancy
    • Progresses to CLL at rate of 1-2%/year

CLL Pathology, cont’d

• CLL characterized by progressive accumulation of mature-looking lymphocytes in blood, bone marrow and lymphatic tissues
  – Cells are functionally immature
  – Cells indistinguishable from those in Small Lymphocytic Lymphoma (different manifestations of the same disorder in WHO classification)
• B-cell neoplasm
  – Positive for CD5 and CD23 cell surface markers
Differential Diagnosis of SLL, CLL and MBL

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral Blood Lymphocytes</th>
<th>Bone Marrow Lymphocyte Infiltration (%)</th>
<th>Extramedullary Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>≥ 5 x 10^9/L (≥ 5,000/mm^3)</td>
<td>≥ 30</td>
<td>Present</td>
</tr>
<tr>
<td>SLL</td>
<td>&lt; 5 x 10^9/L (&lt; 5,000/mm^3)</td>
<td>&lt; 30</td>
<td>Present</td>
</tr>
<tr>
<td>MBL</td>
<td>&lt; 5 x 10^9/L (&lt; 5,000/mm^3)</td>
<td>&lt; 30</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Hematology Oncology Clinics Oct 2008

Two Staging Systems

- Binet – more commonly used in Europe
  - Stage A: No anemia or thrombocytopenia, fewer than three areas of lymphoid involvement
  - Stage B: No anemia or thrombocytopenia, three or more areas of lymphoid involvement
  - Stage C: Anemia (hemoglobin < 10 g/dl) and/or thrombocytopenia (< 100 x 10^9 or < 100,000/mm^3), regardless of the number of areas of lymphoid involvement
Rai Staging System

Stage 0: Lymphocytosis > 5 x 10⁹ (>5,000/mm³)
Stage I: Lymphocytosis with lymphadenopathy
Stage II: Lymphocytosis with hepatomegaly or splenomegaly, with or without lymphadenopathy
Stage III: Lymphocytosis with anemia (Hemoglobin < 11 g/dL) with or without lymphadenopathy, hepatomegaly or splenomegaly
Stage IV: Lymphocytosis and thrombocytopenia (<100,000/mm³), with or without other features

Median Survival by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rai Stage 0</td>
<td>14.5</td>
</tr>
<tr>
<td>Rai Stage I &amp; II</td>
<td>7.5</td>
</tr>
<tr>
<td>Rai Stage III &amp; IV</td>
<td>2.5</td>
</tr>
<tr>
<td>Binet Stage A</td>
<td>14</td>
</tr>
<tr>
<td>Binet Stage C</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Hematology Oncology Clinics Aug 2009
Other Unfavorable Prognostic Factors

- Advanced age
- Male gender
- Lymphocyte doubling time < 12 months
  - Shortened median survival time (36 months)
- Beta 2 microglobulin elevated
  - Reflects tumor burden and cell turnover rate
- CD38 positivity (≥ 30% of leukemic cells)

Cytogenetic Abnormalities

- Using fluorescence in-situ hybridization (FISH) cytogenetic abnormalities present in 82% of CLL patients
- Favorable: 13q deletion as sole abnormality
- Neutral: Trisomy 12
- Unfavorable:
  - 17p deletion – very aggressive clinical course
  - 11q deletion
IgV<sub>H</sub> Gene Mutation

- Mutations in immunoglobulin heavy chain variable gene (> 2% difference from germline) are associated with longer survival
  - Seen in approximately 50% of CLL patients
  - Median survival of 293 months versus 95 months for patients with unmutated IgV<sub>H</sub> (Hamblin et al *Blood* 2005;94: 1848-54)
- Determination requires DNA sequencing
  - Expensive, and not readily available
Next best thing: ZAP-70

• Zeta chain associated protein 70 – a tyrosine kinase involved in cellular signaling in T cells
  – Measured by flow cytometry, which is widely available
• Abnormally expressed in malignant B cells of some patients with CLL
  – Said to be overexpressed when present in >20% of cells
• Overexpression correlates with unmutated IgV\textsubscript{H} and and portends similarly worse prognosis

Treatment of CLL/SLL

• Watchful waiting appropriate for many asymptomatic patients without rapid disease progression
  – Exception: Patients with 17p deletions
  – In other patients, indications for treatment include systemic symptoms, progressive marrow failure, autoimmune cytopenias, massive splenomegaly or lymphadenopathy and rapid lymphocyte doubling time
• Radiation therapy – treatment of choice for rare patients with Ann Arbor Stage 1/2 SLL
  – 10 yr relapse-free survivals of 80% for stage 1 and 62% for stage 2 (Morrison et al, J Clin Oncol 1989)
Chemotherapy for CLL

- Effectiveness varies with prognostic factors
  - Palliative, not curative
- Multi-agent: alkylator + nucleoside analog
  - Fludarabine and cyclophosphamide (FC) most often used
- Single agents used in more frail patients
  - Chlorambucil, fludarabine, bendamustine all have good activity as single agents
- Immunomodulatory drugs (lenalidomide) also active as single agents and in combination with immunotherapy (monoclonal antibodies)

Monoclonal Antibodies

- Rituximab – acts against CD20 cell surface antigen, which is present on > 90% of mature B-cell leukemias and lymphomas
  - Has single agent activity against CLL
  - Most often combined with FC --> FCR
    - Standard of care in young (< 70 years) healthy patients
    - Response rates of 76% with progression free survival rates of about 40 months in clinical trials (Shansal M, Haddad R, Dis Mon 2012)
- Alemtuzumab – anti-CD52 agent recently approved for CLL
  - Effective agent; studies ongoing
  - Combined with high dose methylprednisolone, is a good first-line treatment for patients with 17p deletion
Stem Cell Transplantation

• Usually reserved for younger patients with unfavorable features (unmutated IgV<sub>H</sub>, 17p or 11q deletions)

• Allogeneic Hematologic Cell Transplantation (allo-HCT) most effective
  – Graft-vs-leukemia effects of donor cells largely responsible, but also cause undesirable graft-versus-host disease issues
  – Reduced intensity conditioning programs decrease transplant related mortality but may increase relapse risk

• Durable remissions (cures) are possible

Case Study Wrap-Up

• Unfavorable features:
  – Male, 13 years into course of disease
  – Rai stage II (Binet B) with early thrombocytopenia
  – High β-2 microglobulin

• Favorable features:
  – Cytogenetics (13q deletion) and low CD38 and ZAP-70
  – Age?
  – Excellent response to GA-101 (obinutuzumab), a 3rd generation anti-CD20 monoclonal antibody
    • Early studies look like it may be more effective against B-cell malignancies than rituximab
    • Long term survival statistics not yet available
CLL - Summary

- Most common form of leukemia in USA
- Usually presents at ages > 60 years
- Course is often quite indolent, but can occasionally be progressive over far fewer years
- Best cases characterized by:
  - Early stage (Rai 0, Binet A)
  - Slow lymphocyte doubling time
  - Cytogenetics normal, trisomy 12 or 13q deletion as sole abnormality
  - IgVH mutated; low ZAP-70, CD-38 and beta-2-microglobulin
- Survivals are improving with newer treatments, but most still considered palliative, as few cases are cured

The doctor gave a woman six months to live.

She couldn’t pay her bill, so she gave her another six months!